UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/819,464	03/28/2001	Martin Friede	B45070-1 US1	1150

23347 7590 10/27/2009

GLAXOSMITHKLINE
CORPORATE INTELLECTUAL PROPERTY, MAI B482
FIVE MOORE DR., PO BOX 13398
RESEARCH TRIANGLE PARK, NC 27709-3398

EXAMINER	
LUCAS, ZACHARIAH	

ART UNIT	PAPER NUMBER
1648	

NOTIFICATION DATE	DELIVERY MODE
10/27/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USCIPRTP@GSK.COM
LAURA.M.MCCULLEN@GSK.COM
JULIE.D.MCFALLS@GSK.COM

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/819,464
Filing Date: March 28, 2001
Appellant(s): FRIEDE ET AL.

Michael M. Conger
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed August 17, 2009 appealing from the Office action mailed July 8, 2008.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is substantially correct.

However, in addition to the claims listed in the Appendix to the Appeal Brief, an additional claim 96 was submitted as has been cancelled from the application.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Lipford et al., "Vaccination with immunodominant peptides encapsulated in Quil A-containing liposomes induces peptide-specific primary CD8+ cytotoxic T cells," Vaccine, vol 12, no. 1 (January 1994), pp. 73-80.

5,583,112	Kensil et al.	12-1996
WO 94/00153	Prieels et al.	01-1994

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

I. Claims 74-76, 78, 80, 82-84, 94, and 95 stand rejected under 35 U.S.C. 103(a) as being unpatentable over the teachings of Lipford and of the teachings of Kensil. Claims 74-76 and 95 describe compositions comprising an antigen, the saponin QS-21, and sterol (preferably cholesterol) in an excess by weight to the saponin of less than 1:100 w/w, preferably within the range of 1:2 to 1:100 (claim 75). Claim 95 further specifies that the ratio is between above 1:1 and about 1:5 w/w. Claims 78 and 80 further require the presence of either aluminum hydroxide or aluminum phosphate. Claim 82 requires the use of a QS21 saponin of at least 98% purity. Claim 83 requires that the sterol and saponin be in the form of a vesicle like structure. Claim 94 is drawn to the compositions of claim 83, wherein the structures are unilamellar liposomes. Claim 84 identifies a specific antigen (here, Plasmodium antigen) to be included in the composition.

It is noted that the Appellant has separately argued the motivation for combination in the rejection of claim 95. However, upon consideration of the Appellant's arguments in the Appeal Brief on pages 9-12, regarding claims 74-76, 78, 80, 82-84, and 94 the basis previously applied to these claims is modified such that the rejection of these claims also relies on the routine optimization argument presented in the record and argued in the Brief with respect to claim 95.

Thus, the first and third grounds of rejection in the Brief are considered as a single basis for rejection in this Answer.

Lipford teaches the making of immunogenic compositions comprising cholesterol based liposomes (unilamellar liposomes) and the saponin adjuvant Quil A. Abstract, page 74. Thus, the reference teaches a method of combining an excess of cholesterol to saponin formulation with a ratio of about 1:12.5. Lipford teaches the liposomes as an alternative to known saponin/cholesterol compositions known as ISCOMs. However, the reference does not teach the use of purified QS-21.

Kensil teaches that QS-21 (referred to as QA-21 in the reference) is component of Quil A. The reference teaches that QS-21 has adjuvant properties comparable to or greater than Quil A (cols 6, and 22-23). Kensil also teaches that the purified saponins of the patent (including QS-21) showed adjuvant effects at lower dosages than the crude saponin extract (Quil A). Columns 3-4, and col. 6, lines 30-40. Further, the reference teaches that these purified saponins tend to be less toxic (have less hemolytic activity) than the Quil A extract. Columns 3-4 and column 20. Thus, the art provides several reasons for the substitution of the Quil A components, including QS-21, for Quil A in the compositions of Lipford. It would therefore have been obvious to those of ordinary skill in the art to substitute the purified saponins of Kensil, one of which is QS-21, for the crude Quil A extract used in Lipford.

Further, those of ordinary skill in the art would have had a reasonable expectation of success in the combination. This is because Lipford states that there are two aspects of ISCOM important to their activity- the liposome structure and the adjuvant properties of Quil A. Page 78, second full paragraph. The teachings of Kensil indicate that the properties Lipford identified for

Quil A are also indicative of adjuvant properties of saponins in general. Column 12, lines 21-30. Thus, Kensil suggests that the fractions of Quil A, including QS21, would have these properties. Kensil also suggests that saponins may be incorporated into liposomes. . See e.g., column 11, lines 27-29. Because Kensi indicates that QS-21 shares the required properties with the crude Quil A extract, those of ordinary skill in the art would also have had a reasonable expectation of success in the substitution of QS-21 for Quil A in the liposomes of Lipford. The combined teachings of these references therefore render the indicated claims obvious

It is noted that while the references do not teach the specific purity of QS-21 as required by claim 82, such would have been an obvious optimization of the claimed inventions, particularly in view of the teachings of Kensil indicating that the purified saponins are less toxic that the crude extract. Thus, the limitation of new claim 82 (requiring 98% purity) is therefore an obvious optimization of the composition suggested by the Lipford and Kensil references.

In addition, the Lipford reference teaches that the adjuvant composition disclosed therein may be used to enhance the immune response against peptide antigens in general. Abstract. Kensil supports these teachings, and identifies examples of target antigens with which saponin adjuvants can be used. Column 10, lines 38-50. Among the examples of antigens identified by Kensil are antigens from a Plasmodium protozoan.

Neither of the cited references specify the combination of the QS-21 with a sterol in the ratios of the rejected claims. As was indicated above, claim 95 is drawn to the saponin sterol composition wherein the ratio by weight of the saponin to sterol is between above 1:1 and about 1:5. This claim was rejected on the basis of routine optimization of a composition suggested by

the applied prior art. Independent claim 74, and claim 75, as described above also provide for broader ranges of saponin/sterol ratios that are inclusive of the ranges of claim 95. For the reasons indicated above, the basis of rejection applied to claim 95 is extended to the other claims (claims 74-76, 78, 80, 82-84, and 94) on the basis that the ratios of claims 74 and 75 would also be obvious by routine optimization.

With respect to the routine optimization, it is noted that the teachings of Kensil indicate that QS-21 has somewhat reduced hemolytic activity compared to Quil A. Figure 11. Second, Lipford indicates that the hemolytic activity of saponins appear to be due, at least in part, to its ability to intercalate with cholesterol containing membranes. Page 78, left column. From these teachings, it would be obvious to those of ordinary skill in the art that the presence of the cholesterol in ISCOMs may at least partially responsible for the reduced hemolytic activity of the saponin in the ISCOM formulation. As Lipford teaches that the liposomal structures disclosed in the reference are alternatives to such ISCOMs, and as the reference indicates that the liposomal structure of ISCOMs is important to ISCOM activty (page 78, second paragraph under discussion), the teachings of this reference also indicate that the same effects would have been expected regarding the liposome/saponin formulations suggested by the reference.

Thus, in view of the teachings of Kensil indicating that the hemolytic properties of the Quil A fractions vary from those of Quil A itself, it would have been obvious to those of ordinary skill in the art to vary the amount of cholesterol in the liposomal formulations of Lipford to determine the optimal concentration of sterols required to minimize the hemolytic activity of the saponin. I.e., it would have been obvious to those of ordinary skill in the art to use

routine optimization to optimize the ratio of QS-21 to cholesterol in the compositions suggested by the references.

II. Claims 77, 79, and 81 stand rejected under 35 U.S.C. 103(a) as being unpatentable over the teachings of Lipford and Kensil, further in view of Prieels. These claims are drawn to embodiments of the previously described claimed compositions, wherein the compositions further include a derivative of an enterobacterial lipopolysaccharide, particularly 3-o-deacylated monophosphoryl lipid A (3D-MPL). Claim 81 requires the presence of 3d-MPL in combination with aluminum hydroxide or aluminum phosphate.

In addition to the teachings described above, Kensil also teaches that the adjuvant saponins described therein may be combined with additional adjuvants. See e.g., column 8-9 (esp. column 8, lines 41-45- indicating that purified saponins may be combined with other adjuvants, such as aluminum based adjuvants). However, neither of Lipford or Kensil teaches or suggests the combination of the saponins with 3D-MPL.

However, the teachings of the Prieels reference demonstrate a synergy in the use of both QS-21 and 3D-MPL as adjuvants. Whole document. In addition to combinations of QS-21 and 3DMPL, the reference also teaches the inclusion of aluminum salts. Pages 12-14. Thus, from these teachings, it would have been obvious to those in the art to include 3D-MPL, or 3D-MPL and an aluminum salt, in the liposome formulations comprising QS-21. Those in the art would have had a reasonable expectation of success in the combination based on the teachings in Prieels that such combinations would be effective.

(10) Response to Argument

The Appellant's Brief provides three basis of traversal for the rejection of the claims. It is noted that the same grounds are asserted with respect to each of claims 74-76, 78, 80, 82-84, 94, and 95 over the teachings of Lipford and Kensil, and claims 77, 79, and 81 over these references further in view of Prieels. These rejections are therefore considered together.

In addition, as was indicated above the Appellant's arguments on pages 9-12 of the Brief are found persuasive in part. As was also indicated above, the rejection of the other claims was therefore modified so as to rely on the routine optimization argument previously presented, and argued, with respect to claim 95. Thus, the arguments presented with respect to this claim are considered as applying to each of the rejected claims.

Thus, considering that the arguments presented on pages 9-12 are considered moot in view of the restated rejections, and that the arguments with respect to claim 95 are now considered to apply to the claims generally, the Appeal Brief is considered to provide two general arguments in traversal of the rejections.

First, the Appellant asserts that the teachings of the art fail to provide a motivation to combine the teachings of Lipford and Kensil.

Second the Appellant asserts that the claimed ratios of saponin to sterol would not have been obvious through routine optimization of the compositions suggested by the cited prior art.

I. The combined teachings of Kensil and Lipford, or of these references in combination with Prieels, render obvious the use of QS-21 in liposome compositions such as are described by Lipford.

The Appellant asserts that the teachings of Kensil and Lipford fail to render obvious the claimed compositions in part because there is no motivation to combine the teachings of the reference. The Appellant provides two related arguments in support of the assertion. First, the Appellant asserts that there is no motivation in the cited art for the use of a sterol composition to deliver the QS-21 saponin adjuvant. Second, the Appellant asserts that there are no teaching in the prior art suggesting that those of ordinary skill in the art would use QS-21 as a substitute for Quil A (the saponin adjuvant used in Lipford). These arguments should not be found persuasive for the reasons indicated below.

1) The art provides motivation for the use of a sterol composition for the delivery of the QS21 saponin adjuvant.

Appellant's first argument in traversal of the rejection is that there is not motivation for the combination of a sterol when QS21 is used as the saponin adjuvant. In particular, the Appellant asserts that the application teaches necrosis associated with administration of QS21 in simple solution, and the resolution of the problem by combining the saponin with a sterol. App Br, pages 6-7. The Appellant further asserts that the cited prior art fails to recognize the necrotic reactogenicity of the QS-21 adjuvant. Id. The Appellant therefore concludes that because the present claims combine the sterol with the saponin to avoid the necrotic activity, and as the prior art fails to recognize this activity, the prior art fails to provide a motivation for the combination of the saponins of Kensil with the cholesterol liposomes of Lipford. The argument should not be found persuasive.

It is first noted that the Examiner need not rely on the same motivation as the Appellant for motivation to combine various teachings in the art. See e.g., *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985- indicating that the fact that Appellant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious). I.e., the fact that the Appellant combined the sterol with the saponin to reduce its necrotic activity does not necessarily render the claimed invention non-obvious if the Examiner has provided other grounds for combining these elements.

During the course of prosecution, it was noted that QS21 was disclosed in Kensil as having hemolytic activity. See, the Response of January 2007, and Kensil, column 20 lines 21-41. Thus, while the prior art may not have recognized the necrosis referred to by the Appellant, the reference clearly indicates that QS21 is reactogenic in that it induces hemolysis. Moreover, as was indicated in the statement of the rejection above, Lipford indicates that the hemolytic activity of saponins appear to be due, at least in part, to its ability to intercalate with cholesterol containing membranes. Because both references note the reactogenicity of the adjuvant, and as Lipford suggests a cause for the hemolytic activity, these combined teachings would have suggested to those of ordinary skill in the art a motivation for the combination of QS21 with a sterol (i.e. to reduce its hemolytic effects) when it is to be administered as an adjuvant. Becasue the teachings of the art provide a motivation for the combinatoin of QS21 with a sterol for delivery to reduce its hemolytic effects, the Appellant's argument that the art provides no motivation for the combination should not be found persuasive.

2) The teachings of Kensil provide motivation to substitute the crude Quil A extract with purified QS21 as an adjuvant.

On page 8-9 of the Appeal Brief, the Appellant argues that the Examiner relied on three assertions to provide motivation for the substitution of QS21 for Quil A in the compositions of Kensil and Lipford, and that the teachings of the art fail to support any of these assertions. These assertions are as follows:

(1) QS21 has adjuvant effect equal to or greater than Quil A.

(2) purified saponins show adjuvant effects at lower doses than crude saponins, and

(3) purified saponins are less toxic (hemolytic) than Quil A.

The Appellant asserts that statement (1) is not supported by the teachings in the art; and that the assertions (2) and (3), which apply to purified saponins generally, fail to provide motivation to use purified QS-21.

A) The teachings of Kensil suggest that QS21 has adjuvant effect equal to or greater than Quil A.

The first assertion noted by the Appellant is that QS21 has adjuvant effect equal to or greater than Quil A. The Appellant indicates that the reference does not provide a direct comparison between the adjuvant effects of Quil A and QS21. Appellant asserts that because there is no such direct comparison, the teachings of the reference fail to support the assertion that QS-21 has equal or improved adjuvant activity relative to unpurified Quil A.

It is acknowledged that the reference does not verbatim compare QS-21 directly to Quil A. However, while the reference may not have provided a direct comparison, Kensil does

indicate that purified saponin fractions, including QS21, showed adjuvant effects at lower dosages that the crude extract (i.e. Quil A). See e.g., page 4 of the action mailed on August 10, 200; and Kensil, column 5 lines 20-32 (teaching the adjuvant effective dose of Quil A as about 9-23 μg of carbohydrate); and column 6 lines 30-40 (teaching the adjuvant effective dose of QS21 as about 4.5 μg or less of carbohydrate). Thus, the teachings of Kensil clearly suggest that QS21 has improved adjuvant activity over the crude Quil A extract.

B) The teachings of Kensil provide motivation to use purified saponins generally, including QS21 specifically, as substitutes for Quil A in adjuvant formulations.

The Appellant asserts that the generic teachings of Kensil with respect assertions (2) and (3) regarding purified saponins generally fail to provide a motivation to specifically use QS-21 as a substitute for Quil A. The argument should not be found persuasive.

While the teachings of Kensil are general to the purified saponins, the reference supports such teachings with data relating to the specific saponins. For example, with respect to assertion (2), it is noted that while the teachings of Kensil do indicate that the purified saponins generally show adjuvant effects at lower doses than Quil A, the reference supports this with teachings that specifically indicate that the statement applies to QS-21. See e.g., the description of columns 5 and 6 of the Kensil reference above.

With respect to assertion (3), the Appellant asserts that Kensil fails to indicate that QS-21 is in fact less toxic than Quil A. App Br, page 9 (noting that Kensil teaches in column 2 that each of Quil A and QS21 cause hemolysis at concentrations as low as 25 μg/ml). However, even with respect to this, the conclusions of the reference are based on data presented in the reference

which indicate that QS-21 shows reduced toxicity relative to Quil A, albeit maybe not as significant a reduction as other purified fractions. See e.g., Figure 12. In particular, Figure 12 indicates that Quil A (represented by the line with empty circles) showed greater hemolysis than QS21 (represented by the line with empty squares). Further, even if the data indicates that QS21 is only marginally less toxic than Quil A, it must also be remembered that the reference teaches that QS21 is an effective adjuvant at lower doses. Because it may be administered at lower doses, it would be apparent to those of ordinary skill in the art that this would offset the only mildly less toxic effects of the saponin relative to Quil A at equivalent dosages. In addition, it is also noted that column 27 of the reference indicates that QS-21 specifically showed less general toxicity than Quil A.

The teachings of the reference are therefore not general to purified saponins as suggested by the Appellant. Rather, the reference provides general statements regarding the purified fractions, which general statements are supported by teachings regarding the fractions, including QS-21, individually. The teachings of the reference therefore provide motivation for the substitution of QS-21 for Quil A for the reasons indicated in the assertions identified by the Appellant.

Moreover, as was indicated in the action of February 22, 2006, regardless of the teachings in Kensil regarding the operability of QS21 in comparison to Quil A, the reference does indicate that the compound has adjuvant activity. Thus, because the art indicates that both Quil A and QS21 are adjuvants (Kensil, column 6) and are thus functional equivalents (see MPEP § 2144.06), it would have been prima facie obvious to substitute one with the other.

Because the teachings of the art indicate that QS21 would a suitable substitute adjuvant to Quil A; indicate that QS-21 has greater adjuvant activity (e.g. by showing adjuvant activity at lower doses) than Quil A; and indicate that QS-21 is less toxic, including less hemolytic, than Quil A, the Appellant's traversal on the grounds that the art does not support the relied on assertions and that the reference provides inadequate data relative to QS21 should not be found persuasive.

II) The claimed ratios of saponin to sterols would have been obvious through routine optimization of the compositions suggested by the prior art.

The Appellant's second argument in traversal of the rejection is that the teachings of the prior art fail to render obvious the claimed inventions as they do not suggest the optimization of ratio of the sterol to the QS-21 saponin. The Appellant appears to provide two assertions in support of the argument.

First, on pages 9, 12, and 14-15 of the Appeal Brief, the Appellant asserts that the teachings of the cited art fail to render obvious the claimed ratios through routine optimization. In particular, the Appellant correctly asserts that a ratio may only be obvious through routine optimization where the variable is a result-effective variable. The Appellant then asserts that the Examiner has not suggested any result that may be made through the optimization of the ratio of sterol to saponin.

However, as noted in the Advisory action of December 22, 2008, and in the statement of the rejectoin with respect to claim 95 above, the combined teachings of Kensil and Lipford do suggest a result-effective basis for such optimization. In particular, by teaching the hemolytic

acitivity of the saponins, and indicating that this activity arises from the incalation of the saponin in cholesterol containing membranes, the teachings in the art suggest that the hemolytic activity of the saponins in the compositions of the references is counteracted by the presenec of cholesterol in the cholesterol/saponin formulations described. While the explicit teachings of the references are, as asserted by the Appellant on page 10 of the Brief, silent as to the importance of the ratio of the saponin to the sterol, the teachings of the reference nonetheless suggest to those of ordinary skill in the art the optimization of the ratio for the reasons previously indicated. Thus, those of ordinary skill in the art would be motivated to optimize the amount of cholesterol relative to the saponin in the compositions for the pirpose of minimizing the toxic effects of the saponin adjuvants. This argument in traversal should therefore not be found persuasive.

It is additoinally noted that on pages 13-14 of the Appeal Brief, the Appellant notes that the Examiner basis the arguments based on teachings found in Lipford with respect to ISCOMs, and indicates in the Advisory action that the reference renders obvious the optimization of the cholesterol to spaonin ratio in ISCOMs. The Appellant therefore questions the applicability of these teachings to the non-ISCOM formulations of the present claims.

With respect to these assertions, it is noted that the statements of the Advisory action were clearly made in support of the rejection of record, which record also clearly notes that the present claims are not directs to ISCOMs. See e.g., pages 3-4 of the action mailed on February 22, 2006. Moreover, it is noted that the liposome/saponin compositions of Lipford maintain the same elements of the ISCOMs, and are identified as an alternative form to such ISCOMs. Moreover, as was noted in the action of August 5, 2005, Lipford identifies the liposomal

structure and presence of the saponin as the two aspects of ISCOMs required for their activity. August 2005 action, page 5; Lipford, page 78. These aspects are shared by the liposomes taught by the reference. Thus, those of ordinary skill in the art would have had a reasonable expectation that the characterstics and modes of activity of ISCOMs related by Lipford could be equally applied with respect to the described lipsome compositions.

The reference to optimization in ISCOMs rather than liposomes in the final Advisory action was clearly a mistake when considered in light of the record; and the teachings of Lipford relating to ISCOMs would have been understood by those of ordinary skill in the art to also apply to the liposomes suggested by the reference as an alternative to such ISCOMs, but which share the same essential features (i.e. lipsomal structure and the saponin adjuvant). The assertions on pages 13-14 of the Brief should therefore also not be found persuasive.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,
/Zachariah Lucas/
Primary Examiner, Art Unit 1648

Conferees:

/Robert B Mondesi/
Supervisory Patent Examiner, Art Unit 1645
/Larry R. Helms/
Supervisory Patent Examiner, Art Unit 1643